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[Overview of Reviews]

Rehabilitation for people with multiple sclerosis: an overview of Cochrane Reviews

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ABSTRACT

Background

Multiple sclerosis (MS) is a major cause of chronic, neurological disability, with a significant long-term disability burden, often requiring comprehensive rehabilitation.

Objectives

To systematically evaluate evidence from published Cochrane Reviews of clinical trials to summarise the evidence regarding the effectiveness and safety of rehabilitation interventions for people with MS (pwMS), to improve patient outcomes, and to highlight current gaps in knowledge.

Methods

We searched the Cochrane Database of Systematic Reviews up to December 2017, to identify Cochrane Reviews that assessed the effectiveness of organised rehabilitation interventions for pwMS. Two reviewers independently assessed the quality of included reviews, using the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) tool, and the quality of the evidence for reported outcomes, using the GRADE framework.

Main results

Overall, we included 15 reviews published in the Cochrane Library, comprising 164 randomised controlled trials (RCTs) and four controlled clinical trials, with a total of 10,396 participants. The included reviews evaluated a wide range of rehabilitation interventions, including: physical activity and exercise therapy, hyperbaric oxygen therapy (HBOT), whole-body vibration, occupational therapy, cognitive and psychological interventions, nutritional and dietary supplements, vocational rehabilitation, information provision, telerehabilitation, and interventions for the management of spasticity. We assessed all reviews to be of high to moderate methodological quality, based on R-AMSTAR criteria.

Moderate-quality evidence suggested that physical therapeutic modalities (exercise and physical activities) improved functional outcomes (mobility, muscular strength), reduced impairment (fatigue), and improved participation (quality of life). Moderate-quality evidence suggested that inpatient or outpatient multidisciplinary rehabilitation programmes led to longer-term gains at the levels of activity and participation, and interventions that provided information improved patient knowledge. Low-quality evidence suggested that neuropsychological interventions, symptom-management programmes (spasticity), whole body vibration, and telerehabilitation improved some patient outcomes. Evidence for other rehabilitation modalities was inconclusive, due to lack of robust studies.

Authors' conclusions

The evidence suggests that regular specialist evaluation and follow-up to assess the needs of patients with all types of MS for appropriate rehabilitation interventions may be of benefit, although the certainty of evidence varies across the different types of interventions evaluated by the reviews. Structured, multidisciplinary rehabilitation programmes and physical therapy (exercise or physical activities) can improve functional outcomes (mobility, muscle strength, aerobic capacity), and quality of life. Overall, the evidence for many rehabilitation interventions should be interpreted cautiously, as the majority of included reviews did not include data from current studies. More studies, with appropriate design, which report the type and intensity of modalities and their cost-effectiveness are needed to address the current gaps in knowledge.

PLAIN LANGUAGE SUMMARY

Rehabilitation for persons with multiple sclerosis

Review questions

Do people with multiple sclerosis (MS), who participate in rehabilitation programmes, improve in their functional activities, disability, and quality of life compared with those who receive no rehabilitation treatment, placebo, or different types of interventions?

Background

MS is a complex condition, which requires comprehensive, long-term management. Rehabilitation programmes aim to improve function, well-being, and quality of life for people with MS. Currently, a wide variety of rehabilitation therapies are used to treat MS. Published literature, including Cochrane Reviews, that evaluates these interventions, has grown. To guide clinicians, this review assessed current Cochrane Reviews, and provides an overview of the effectiveness of rehabilitation therapies used to treat people with MS.

Study characteristics

We searched for all published Cochrane Reviews of MS clinical trials that evaluated the effectiveness of rehabilitation interventions compared with various control groups (no intervention or different type of intervention). We evaluated all relevant reviews, and summarised the findings.

Key results and quality of evidence

We included a total of 15 Cochrane Reviews, which included 168 clinical trials, and a total of 10,396 people with MS. These good-quality reviews evaluated a range of rehabilitation interventions, including: physical activity and exercise therapy, hyperbaric oxygen therapy, whole-body vibration, occupational therapy, cognitive and psychological interventions, nutritional and dietary supplements, vocational rehabilitation, information provision, telerehabilitation, and interventions for the management of spasticity.

The findings showed some benefits for people with MS who participated in exercise and physical activity programmes or multidisciplinary rehabilitation programmes (where the intervention is provided by a team of health professionals from different professions). They found improvements in everyday activities, function, and health-related quality of life, compared with those who were not offered rehabilitation. Evidence for other rehabilitation modalities was limited, due to lack of good-quality studies. More research is needed to determine whether various types of rehabilitation modalities are effective in reducing disability in people with MS.

BACKGROUND

Description of the condition

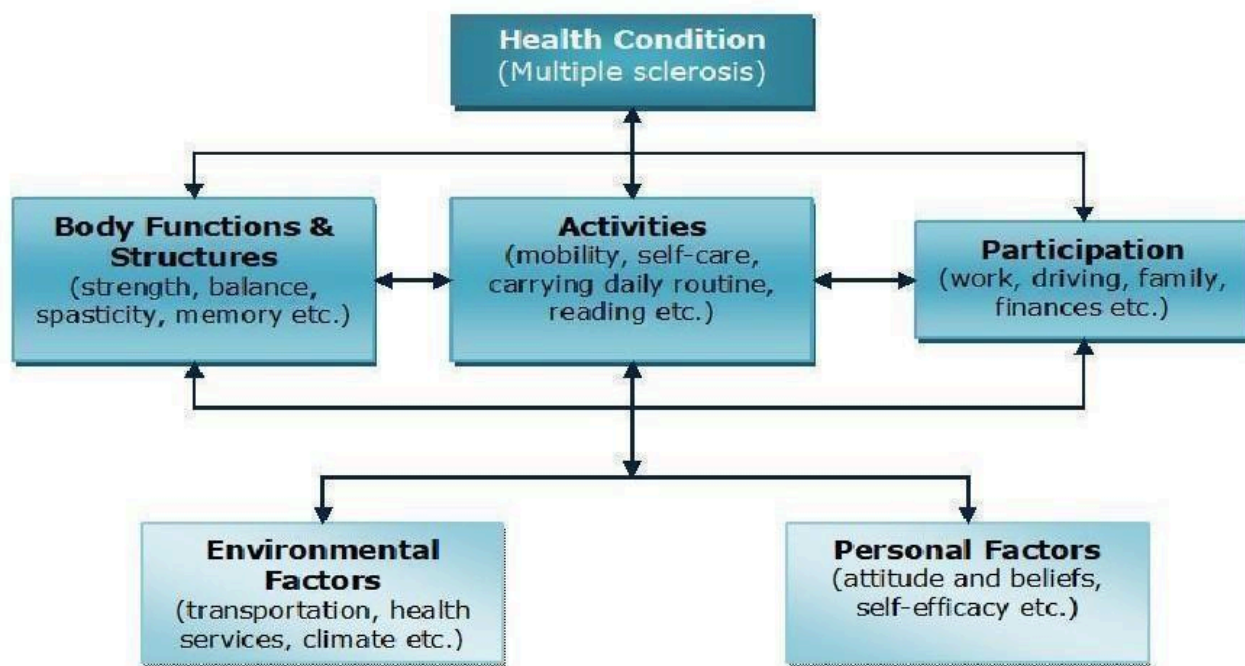
Multiple sclerosis (MS), an autoimmune inflammatory demyelinating disease of the central nervous system, is a major cause of chronic neurological disability in young and middle-aged adults (aged 18 to 50 years (Barten 2010)). MS affects approximately 1.3 million people worldwide, with a median estimated incidence of 2.5 per 100,000 (range 1.1 to 4) globally (WHO 2008). The global prevalence rate of MS is estimated to be 30 per 100,000 (range 5 to 80), with a female preponderance (female to male ratio of 3:1 (Trisolini 2010; WHO 2008)). MS is characterised by significant variability in presentation and prognosis, and is associated with complex disabilities, including disorders of strength, sensation, co-ordination and balance, visual, and cognitive deficits (Beer 2012; Khan 2007a; Khan 2007b). These impairments usually lead to progressive limitation of functioning in daily life and require long-term multidisciplinary management. Factors associated with worse prognosis are: older age at onset, progressive disease course, multiple onset symptoms, pyramidal or cerebellar symptoms, and a short interval between onset and first relapse (Hammond 2000).

MS has an unpredictable disease course and varied patterns of presentation, which include: 'relapsing-remitting' MS (80% of all MS

cases), characterised by exacerbations and remissions, which may convert to a 'secondary-progressive' form of MS with progressive disability between attacks; 'primary-progressive' MS (15% of all MS cases), where progressive disability develops from onset; and 'progressive-relapsing' MS (5% of all MS cases), where the disease worsens gradually and subsequently results in discrete attacks (Amatya 2013; Khan 2007b).

People with MS (pwMS) can present with various combinations of functional deficits, such as physical disability (motor weakness, spasticity, sensory dysfunction, visual loss, ataxia, etc.), fatigue, pain, incontinence, cognitive deficits (memory, attention, executive dysfunctions), psychosocial, behavioural, and environmental problems. These have a multidimensional impact on a person's activity (function) and participation (Khan 2006; Khan 2007b). The International Classification of Functioning, Disability and Health (ICF) provides a global conceptual framework to categorise abilities and problems of persons with different health conditions, within a standard system (WHO 2001). It offers a common language for clinicians to describe functioning, disability, and health of an individual (WHO 2001). A simulated case example of the ICF model related to MS is given in Figure 1.

Figure 1. International Classification of Functioning, Disability and Health (ICF) model with case example for multiple sclerosis



Description of the interventions

People with MS have complex care needs, due to the cumulative effects of impairments and disabilities, and the impact of ageing with disabilities, requiring comprehensive disease management, which includes rehabilitation. Medical rehabilitation is "a set of measures that assist individuals who experience (or are likely to experience) disability to achieve and maintain optimal physical, sensory, intellectual, psychological, and social functioning in

interaction with their environment" (WHO 2011). It is a process of delivering a co-ordinated interdisciplinary care programme, comprising a series of therapies, which are often individualised and goal-oriented to meet the specific needs of a patient (Khan 2017). The goal of rehabilitation is to improve functional independence and enhance participation, with emphasis on patient education and self-management (Khan 2015; Beer 2012; WHO 2011).

A comprehensive rehabilitation approach uses a range of individual or combined therapies and treatments (Khan 2007b; Khan 2010; WHO 2008). These include:

- Unidisciplinary therapy, i.e. therapy provided by a single discipline, which may include (but is not limited to): physiotherapy, occupational therapy, strengthening exercises, endurance training, resistance training, stretching, orthotics (splints, garments), casting, hyperbaric oxygen therapy (breathing pure oxygen in a specially designed pressurised room or chamber), transcutaneous electric nerve stimulation (use of electric current produced by a device to stimulate the nerves for therapeutic purposes), hippotherapy (therapy that uses the natural gait and movement of a horse to provide motor, and sensory input), vibration therapy (exercise training using vibratory platforms), vocational rehabilitation, acupuncture, psychological interventions, nutritional interventions (such as polyunsaturated fatty acids, vitamin D), mental practice, educational interventions, and specific rehabilitation programmes (such as, telerehabilitation, fatigue management, upper limb rehabilitation, and spasticity management).
- Multidisciplinary rehabilitation programmes provide a co-ordinated programme delivered by a specialised team of health professionals from two or more disciplines (medical, nursing, physiotherapy, occupational therapy, speech and language therapy, social work, orthotists, and others).

How the intervention might work

With advances in MS management, there has been improvement in survival rates of pwMS. Therefore, issues related to progressive disability (physical and cognitive), psychosocial adjustment, and social reintegration need to be addressed over time (Khan 2007b). In recent years, a range of rehabilitation interventions trialled in pwMS have provided increasing evidence of improved patient outcomes (Bennett 2010; Khan 2011; Khan 2017). Specifically, physical therapeutic modalities, such as physical therapy and exercise, improve muscle power and strength, exercise tolerance, and mobility-related activities (Campbell 2016; Haselkorn 2015; Heine 2015), and exercise-based programmes reduce patient-reported fatigue (Andreassen 2011; Asano 2014; Heine 2015). Other potential benefits associated with physical activities include improvements in strength and muscle activity, improvement in functional capacity (including cardiorespiratory capacity), enhanced cognitive function, and haemodynamic activity (Cruickshank 2015), and neurobiological processes that could promote neuroprotection and neuroplasticity, and reduce long-term disability (White 2008a; White 2008b). These affect multiple sensorimotor processes (visual, vestibular, proprioception) to generate co-ordinated movements that maintain the centre of gravity within the limits of stability, improving balance and gait patterns (Paltamäa 2012).

There is also evidence for multidisciplinary rehabilitation for longer-term gains at the levels of activity (disability) and participation (Khan 2007b). However, other rehabilitation interventions, such as occupational therapy (Steultjens 2003), transcutaneous electrical nerve stimulation (Glinsky 2007), vibration therapy (Kantele 2015), hippotherapy (Bronson 2010), and hyperbaric oxygen therapy (Bennett 2004) have been found to have no, or limited additional benefit in pwMS (Khan 2017).

Why it is important to do this overview

MS is complex and requires a comprehensive, multidimensional approach to disease management that incorporates integrated rehabilitation interventions. The body of research for rehabilitation interventions is growing, and there are currently a number of Cochrane Reviews published on the efficacy and safety of various rehabilitation approaches. However, the published reviews vary in scope and methodology, with different, and at times diverse, conclusions about the effectiveness of the intervention evaluated. However, some review findings overlap with each other, in terms of interventions and comparisons.

Therapeutic values, including benefits and harms, associated with MS rehabilitation interventions need to be established. The most efficacious approaches, timing, and intensity of these interventions, resource requirements, and associated costs require investigation. To our knowledge, to date, no studies have comprehensively evaluated the existing Cochrane Reviews of various rehabilitation interventions in MS. Therefore, a systematic evaluation of the existing evidence from published Cochrane Reviews is required to provide the best evidence on the effectiveness of these interventions, to guide treating clinicians to achieve optimal patient outcomes. This overview can serve as a 'guiding tool' for evidence-based decisions on appropriate management approaches in pwMS, future programme improvement and design, to inform policy and healthcare decision makers, and for future research in MS.

OBJECTIVES

To systematically evaluate evidence from published Cochrane Reviews of clinical trials to summarise the evidence regarding the effectiveness and safety of rehabilitation interventions for people with multiple sclerosis (pwMS), to improve patient outcomes, and highlight current gaps in knowledge. Specific questions addressed included:

- Are rehabilitation interventions (unidisciplinary, multidisciplinary, or both) effective in minimising impairment, activity limitation, and participation restriction in pwMS?
- Are rehabilitation interventions (unidisciplinary, multidisciplinary, or both) effective in minimising the burden of care and improving quality of life in pwMS?
- What types of rehabilitation interventions (unidisciplinary, multidisciplinary, or both) are effective in pwMS, and in which setting?

METHODS

Criteria for considering reviews for inclusion

Types of studies

In accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*, we searched the Cochrane Database of Systematic Reviews (up to December 2017) to identify Cochrane Reviews that assessed the effectiveness of organised rehabilitation interventions (unidisciplinary, multidisciplinary, or both) for pwMS (Becker 2011). We did not update the individual Cochrane Reviews. We listed all published protocols of ongoing Cochrane Reviews of rehabilitation for people with MS in the 'Classification pending references' section, for inclusion in future updates of this overview.

Types of participants

We included all adults (18 years or over), with all subgroups of MS (relapsing-remitting, secondary-progressive, primary-progressive, and progressive-relapsing MS).

Types of interventions

We included all modalities of rehabilitation interventions in pwMS:

- unidisciplinary therapy, e.g. physiotherapy or occupational therapy only, and other interventions (as described in [Description of the interventions](#)).
- multidisciplinary rehabilitation programmes, defined as any co-ordinated therapy programme delivered by two or more disciplines (occupational therapy, physiotherapy, exercise physiology, prosthetics and orthotics, speech and language therapy, diet, and nursing care), in conjunction with medical input (neurologist or rehabilitation medicine physician) that aimed to achieve patient-centred goals ([Khan 2007b](#)).

The settings of rehabilitation programmes included:

- Ambulatory settings: outpatient or day treatment settings, which may be located within private or public hospitals, community rehabilitation centres, or specialist rehabilitation centres.
- Home-based settings (patients' own homes) and community rehabilitation settings.
- Inpatient rehabilitation settings: specialised medical rehabilitation units or hospital wards, where care is delivered 24 hours per day.

Types of outcome measures

Given the varied presentations of MS-related disability, and goals of treatment related to MS severity, we identified diverse outcomes. The list below is not conclusive, as there is a range of outcome measures that can be used to assess a particular domain. Specific outcome measures (subjective or objective) did not form part of the inclusion criteria for this review.

Primary outcomes

We categorised primary outcomes according to the International Classification of Functioning, Disability and Health (ICF ([WHO 2001](#))). These included:

- Function (mobility, activities of daily living (ADL)): e.g. Functional Independence Measure (FIM ([Granger 1990](#))), Timed Up And Go (TUAG ([Podsiadlo 1991](#))), Barthel Index (BI ([Mahoney 1965](#))), 10-metre walk test ([Green 2002](#)), or other subjective measures alone, or in combination.
- Symptoms or impairments, e.g. pain (measured by verbal scores, visual analogue scales), spasticity (using the Modified Ashworth Scale (MAS ([Ansari 2009](#); [Bohannon 1987](#))), and the Tardieu scale ([Ansari 2008](#); [Mehrholtz 2005](#)));
- Restriction in participation, e.g. quality of life (QoL; MS Quality of Life, MSQOL 54 ([Vickrey 1997](#)))

Secondary outcomes

These included specific outcomes that reflected:

- Measure of achievement of intended goals for treatment, e.g. goal attainment scaling or other measure of goal achievement;
- Impact on caregivers (measured with Caregiver Strain Index (CSI ([Robinson 1983](#))));

We reported any adverse events from these interventions. For this review, we defined serious adverse events as those events that result in death, life-threatening adverse experience, inpatient hospitalisation or prolongation of existing hospitalisation (for > 24 hours), disability or permanent damage, and other important medical events ([FDA 2016](#)).

Search methods for identification of reviews

We searched the Cochrane Database of Systematic Reviews (CDSR; 2017, Issue 12 of 12) in the Cochrane Library (searched December 2017, Issue 12 of 12) for all potential reviews. We included all Cochrane Reviews registered in the CDSR that fulfilled the inclusion criteria, and reported a systematic electronic search of literature for a defined period of time. The search strategy is listed in [Appendix 1](#). We did not apply any restriction on publication date.

Data collection and analysis

We adhered to all data collection and synthesis methodology outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Becker 2011](#)). We had no intention to repeat the assessment of eligibility, the assessment of risk of bias, or meta-analyses from the included reviews, nor to identify systematically any additional studies, or to extract additional outcomes from individual studies included in the original Cochrane Reviews ([Higgins 2011](#)).

Selection of reviews

Two review authors (BA, FK) independently screened and short-listed all abstracts and titles of Cochrane Reviews identified by the search strategy for inclusion and appropriateness, based on the selection criteria. They independently evaluated the full text of the review to determine whether it met the inclusion and exclusion criteria. Any disagreement regarding the possible inclusion or exclusion of any review was resolved through discussion with a third review author (MG), and by a final consensus amongst all authors. We did not exclude any published Cochrane Reviews based on methodological quality.

Data extraction and management

Two review authors (BA, FK) independently extracted data from included Cochrane Reviews, using a predefined, customised electronic data extraction form. A third review author (MG) checked all extracted data for accuracy and consistency. The information obtained from the included reviews is presented in [Table 1](#), which comprised review objectives, publication and search date, characteristics of included studies, population characteristics, characteristics of intervention(s) covered within the scope of the review, comparison intervention(s), outcomes (primary and secondary), intervention effects, including the pooled effects, e.g. risk ratios (RRs), odds ratios (ORs), or mean differences (MDs); 95% confidence intervals (CIs), and review limitation ([Higgins 2011](#)). We extracted a narrative text of the results if no meta-analyses were performed, or statistical results were not available. We resolved any discrepancies by a final group consensus.

We did not review the original or primary trials included in the Cochrane Reviews for additional data; we only analysed data presented in the included reviews.

We discussed all outcomes reported in the included studies of the Cochrane Reviews. We accessed the published reports of the individual trials, and had planned to contact individual researchers if any information from the reviews was unclear or missing, however, this was not required.

Assessment of methodological quality of included reviews

Quality of included reviews

Two review authors (BA, FK) independently assessed the methodological quality of each review, using the Revised-Assessment of Multiple Systematic Reviews (R-AMSTAR) appraisal tool (Kung 2010). Similar to the original AMSTAR tool (Shea 2007a; Shea 2007b), the R-AMSTAR tool contains 11 questions for assessing the methodological quality of systematic reviews (Appendix 2; Appendix 3).

We assigned a score of 1 to 4, based on predefined criteria for each item (yes = considered adequate, or no = considered inadequate), to each domain of the R-AMSTAR tool. We used the sum of total scores, which ranged from 11 to 44, to grade overall methodological quality. For this overview, we considered reviews that obtained scores of 40 or higher to be high quality; scores of 30 or higher to be medium quality; and scores below 29 to be low quality (Shepherd 2016). We resolved any disagreements by consensus among all review authors.

Quality of included studies within reviews

We did not assess the risk of bias of individual included studies within reviews. All of our reported study quality was according to the original Cochrane Review authors' assessments.

Quality of evidence in included reviews

We categorised all outcomes according to the ICF into: function (activity), impairment (symptoms), and participation (QoL, psychological outcomes, vocational outcomes). We used the GRADEpro GDT tool to assess quality of evidence for each type of intervention (Balshem 2011; GRADEpro GDT 2015). Two review authors (BA, FK) independently evaluated the quality of the body of evidence, based on the judgements made by the authors of the original Cochrane Reviews, such as by using the information from 'Summary of findings' tables in the included reviews, if provided. We used the GRADE system to assess the following features of the evidence of outcomes.

- Study limitations (risk of bias): internal validity of the evidence.
- Inconsistency: heterogeneity or variability in the estimates of effect across studies.
- Indirectness: degree of differences between population, intervention, comparator, for the intervention and outcome of interest.
- Imprecision (random error): extent to which confidence in the effect estimate is adequate to support a particular decision.
- Publication bias: degree of selective publication of studies.

Both review authors (BA, FK) resolved discrepancies through discussion with the third review author (MG). The quality of evidence was classified, according to Balshem 2011 as:

- High-quality: very confident that the true effect lies close to that of the estimate of the effect.
- Moderate-quality: moderately confident in the effect estimate, such that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low-quality: confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect.
- Very low-quality: very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of the effect.

The evidence for all relevant outcomes is summarised in a 'Summary of findings' table, along with the number of participants and studies addressing each outcomes, and the GRADE rating for each outcome. The GRADE assessments presented in the 'Summary of findings from included reviews' table are judgements made by the review authors of this overview.

Data synthesis

We compiled a narrative description of the characteristics of the included Cochrane Reviews. We considered the differences in participants, interventions, duration of follow-up, and type of data analysis in each review, along with the main findings of the effects of the interventions investigated in the included reviews, based on the GRADE system.

- Effective interventions: we found high-quality evidence of effectiveness for an intervention.
- Promising interventions (more evidence needed): we found moderate-quality evidence of effectiveness for an intervention, but more evidence is needed.
- Ineffective interventions: we found high-quality evidence of lack of effectiveness for an intervention.
- Probably ineffective interventions (more evidence needed): we found moderate-quality evidence suggesting lack of effectiveness for an intervention, but more evidence is needed.
- No conclusions possible: we found low- or very low-quality evidence, or insufficient evidence to comment on the effectiveness of an intervention.

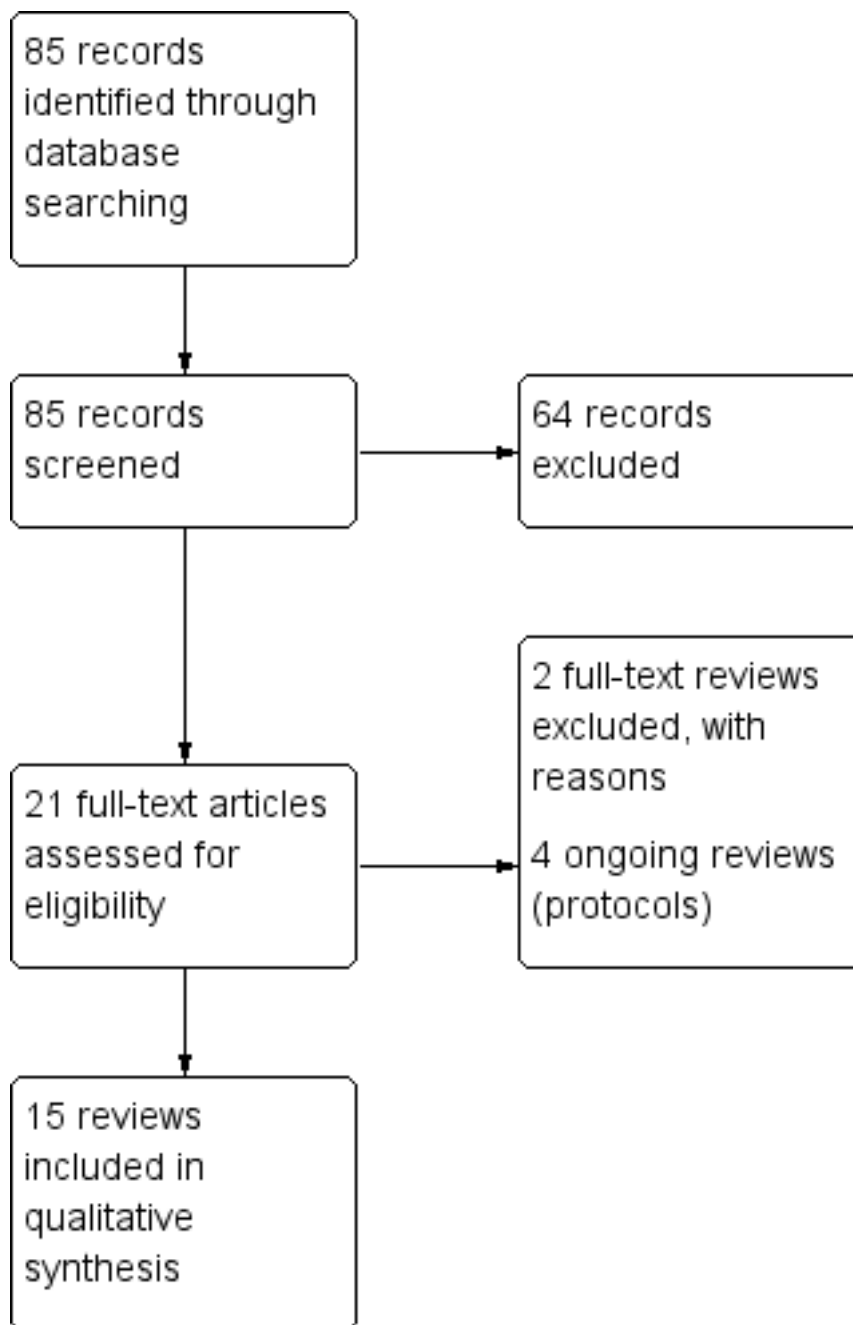
We provided a summary of the results and statistical analysis reported in each included review in summary tables and figures, where possible. As anticipated, we found more than one eligible review of some interventions, such as physical therapy. We reported the common conclusion if these reviews had similar conclusions, and where the conclusions differed, we explored the reasons for any difference in relation to the AMSTAR scores, differences in participants, interventions, duration of follow-up, and type of data analyses in the included reviews. Further, we anticipated some overlap in the trials included among the reviews evaluating similar interventions. In such cases, we compared the results from all reviews and collated the findings, where possible.

RESULTS

The search retrieved 85 published reviews evaluating different interventions currently used in the management of multiple sclerosis (MS). Of these, the majority (N = 64) evaluated pharmacological interventions, and we excluded them. Twenty-one reviews met the abstract inclusion criteria, and we selected them for closer scrutiny. We retrieved the full texts of these reviews, and all review authors performed the final selection. Of these, we excluded two reviews: one review did not provide specific

targeted rehabilitation intervention (Mills 2007), and another did not provide any data for the MS population (Regan 2014). Four reviews were still in the protocol stage (Amatya 2017; Cui 2010; Hayes 2017; Rietberg 2011). Overall, we included 15 reviews in this overview that were published in the Cochrane Database of Systematic Reviews (Amatya 2013; Bennett 2004; das Nair 2016; Farinotti 2012; Heine 2015; Jagannath 2010; Khan 2007b; Khan 2009; Khan 2015; Kopke 2014; Rietberg 2005; Rosti-Otajärvi 2014; Sitjà Rabert 2012; Steultjens 2003; Thomas 2006). We provided a flow diagram of the review selection process in Figure 2.

Figure 2. Study flow diagram



Description of included reviews

The characteristics of the 15 included Cochrane Reviews are summarised in [Table 1](#). The included reviews were published (or updated) between 2003 and 2016. In all reviews, searches were limited to randomised controlled trial (RCT) or clinical controlled trial (CCT) designs, and in three cases, the inclusion was limited to RCTs with follow-up of six months or longer. Overall, these 15 reviews included 164 RCTs and four CCTs, with a total of 10,396 participants.

Methodological quality of included reviews

The results of the R-AMSTAR quality assessment are provided in [Appendix 2](#) and [Appendix 3](#) and total scores for each included reviews are provided in [Table 1](#). The kappa level of agreement between the two review authors for the R-AMSTAR assessment was 0.91. Overall, 11 included reviews were of high methodological quality (R-AMSTAR score ≥ 40), and four were of moderate quality (R-AMSTAR score = 30 to 39 ([Kopke 2014](#); [Rietberg 2005](#); [Sitjà Rabert 2012](#); [Steultjens 2003](#))). The mean R-AMSTAR methodological quality score for included reviews was 39.8 (standard deviation 2.5), and ranged from 34 to 42, out of a possible maximum of 44. All reviews, except one, performed a comprehensive literature search of medical science databases ([Steultjens 2003](#)), however, only half of the reviews included a grey literature search. All reviews, except two, assessed the scientific quality of the included primary studies using validated tools ([Rietberg 2005](#); [Thomas 2006](#)). All reviews provided their funding sources, however, surprisingly, even though the reviewers declared their own conflicts of interest, none addressed the potential competing interests and source of support

of authors of the primary studies. None of the reviews provided an explicit statement on the impact of findings on clinical practice guidelines.

There was heterogeneity amongst the included reviews in the tools used to assess the methodological quality of the primary studies: eight reviews used core items of the Cochrane 'Risk of bias' tool ([Amatya 2013](#); [das Nair 2016](#); [Farinotti 2012](#); [Jagannath 2010](#); [Khan 2015](#); [Kopke 2014](#); [Rosti-Otajärvi 2014](#); [Sitjà Rabert 2012](#)), three used van Tulder's methodological quality checklist ([Khan 2007b](#); [Khan 2009](#); [Steultjens 2003](#)), one used both the PEDro checklist and the Cochrane 'Risk of bias' tool ([Heine 2015](#)), one used the Jadad score ([Bennett 2004](#)), one used a self-designed 11-point checklists ([Rietberg 2005](#)), and [Thomas 2006](#) just used a single item; 'random allocation had been adequately concealed'. The review authors of seven included reviews used the GRADE method to rate the quality of the evidence supported by the primary trials ([Amatya 2013](#); [das Nair 2016](#); [Heine 2015](#); [Khan 2015](#); [Kopke 2014](#); [Rosti-Otajärvi 2014](#); [Sitjà Rabert 2012](#)).

Effect of interventions

A rehabilitation approach to people with MS (pwMS) included a range of treatments and interventions. We summarised the characteristics of included reviews in [Table 1](#), and summarised the best-evidence syntheses for rehabilitation interventions in MS below. We summarised the findings from the included reviews for each type of intervention based on outcomes according to the International Classification of Functioning, Disability and Health (ICF; [Table 2](#)). The summary of the impact of these interventions based on specific settings are shown in [Figure 3](#).

Figure 3. Impact of outcomes of rehabilitation interventions based on the settings of care

Intervention	No studies, participants	Inpatient	Ambulatory	Long-term/ community	GRADE
Multidisciplinary rehabilitation	9 RCTs, 1 CCT, 954				Moderate
Physical therapy	54 RCTs, 2510				Moderate
HBOT	9 RCTs, 504				Low
WBV	4 RCTs, 64				Low
OT	1 RCTs, 2 CCTs, 274				Very low
Neuropsychological	20 RCTs, 986				Low
Cognitive rehabilitation	16 RCTs, 1006				Low
Memory rehabilitation	15 RCTs, 989				Low
Information provision	10 RCTs, 1314				Moderate
Dietary intervention (PUFAs)	6 RCTs, 794				Low
Dietary intervention (Vitamin D)	1 RCT, 49				Very low
Vocational rehabilitation	1 RCT, 1 CCT, 80				Low
Telerehabilitation	9 RCTs, 531				Low
Spasticity management interventions	9 RCTs, 341				Low

* Grade of Recommendation, Assessment, Development and Evaluation GRADE grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Low quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low quality: We are very uncertain about the estimate.

CCT = clinical controlled trial; HBOT = hyperbaric oxygen therapy; OT = occupational therapy; PUFAs = polyunsaturated fatty acids; RCT = randomised controlled trial; WBV = whole body vibration

We found marked heterogeneity of the evaluated interventions and measured outcomes amongst the included reviews. Various specific rehabilitation interventions evaluated in included reviews and key findings are summarized below:

Multidisciplinary rehabilitation (1 review)

[Khan 2007b](#) included 10 trials (9 RCTs and 1 CCT), with 954 participants, which evaluated various types of multidisciplinary rehabilitation in pwMS. The authors reported strong evidence for inpatient multidisciplinary rehabilitation (3 RCTs, N = 217) in producing short-term gains at the levels of activity (disability) and participation. Strong evidence was reported for improvement in disability (total Functional Independence Measure (FIM) and Barthel Index (BI)), and level of participation (London Handicap Scale (LHS), and Human Activities Profile (HAP)). There was moderate-level evidence indicating that inpatient rehabilitation could improve symptoms (Guy's Neurological Disability Scale (GNDS)), self-care and sphincter control (FIM), and mobility and locomotion (wheelchair users only (Amended Motor Club Assessment (AMCA))).

In this review, one RCT evaluated an individualised, multidisciplinary rehabilitation programme provided in inpatient settings compared to outpatient settings (N = 84 participants), and reported limited evidence for short-term gains at the level

of activity (ambulatory status and Incapacity Status Scale (ISS)). There was no evidence at the level of participation and reduction in the need for aids or assistance at home. The trial authors did not report details of participants and interventions, such as length of rehabilitation and contents of the rehabilitation programme. One trial, with two reports (N = 101 participants), compared individualised (three to six weeks), multidisciplinary inpatient (three hours of intensive therapy, with blocks of sessions with physiotherapists, occupational therapists, and other allied health professionals, such as speech therapist, neuropsychologist, and social work as required), or outpatient rehabilitation (similar low intensity programme based on patient needs), with a waiting-list control group, and reported moderate evidence for reduced disability, and bladder impairment outcomes, and improved continence-related quality of life (QoL) and participation. Four RCTs evaluated the effectiveness of outpatient multidisciplinary rehabilitation versus control (N = 351 participants), and found limited evidence for improved impairment, measured by the Expanded Disability Status Scale (EDSS), short-term benefits at the level of activity (FIM), and improved fatigue, mood, and social function. There was no convincing evidence for the cost-effectiveness of any multidisciplinary programmes, or the best 'dose' of therapy ([Khan 2007b](#)).

Physical therapeutic modalities

We identified three Cochrane Reviews that assessed physical therapeutic modalities in pwMS; findings are summarised below.

Exercise (2 reviews)

Two reviews evaluated the effectiveness of different types of exercise programmes (Heine 2015; Rietberg 2005).

Heine 2015 evaluated the effectiveness and safety of exercise therapy on fatigue in pwMS. The authors included 45 RCTs (N = 2250 participants), which evaluated 69 different exercise interventions: endurance training (23 interventions), muscle power training (9 interventions), task-oriented training (5 interventions), mixed training (15 interventions), or other (e.g. yoga (17 interventions)). Of these, 36 trials, with 1603 participants, provided sufficient data for the meta-analysis on fatigue. The review authors reported a significant effect on fatigue in favour of exercise therapy compared to non-exercise control (standardised mean difference (SMD) -0.53, 95% confidence interval (CI) -0.73 to -0.33; $P < 0.01$). Despite the significant heterogeneity between trials ($I^2 > 58\%$) and the overall methodological quality, the combined body of evidence was of moderate quality. In a subgroup analysis, the authors also reported a significant effect on fatigue in favour of exercise therapy compared to no exercise for endurance training (SMD -0.43, 95% CI -0.69 to -0.17; $P < 0.01$), mixed training (SMD -0.73, 95% CI -1.23 to -0.23; $P < 0.01$), and other training (SMD -0.54, 95% CI -0.79 to -0.29; $P < 0.01$). Across all studies, exercise did not seem to be associated with a significant risk of a relapse of MS or adverse events. The authors concluded that exercise therapy (endurance, mixed, or other training) could reduce self-reported fatigue, and could be prescribed for pwMS without harm.

Rietberg 2005 examined the effectiveness of exercise therapy for pwMS on activities of daily living (ADL) and health-related QoL (9 RCTs, 260 participants). Six trials compared exercise therapy with no exercise therapy, while three trials compared two different types of exercise therapy interventions. There was strong evidence that exercise-based rehabilitation improved muscle power, exercise tolerance, and mobility-related activities; moderate evidence that it improved mood; but no evidence for fatigue. Exercise therapy was found to be safe, with no adverse events. The review authors reported that there was no evidence on optimal type, duration, intensity, or frequency of training sessions, due to diversity amongst included trials. The authors concluded that exercise therapy could be beneficial for pwMS who were not experiencing an exacerbation.

Hyperbaric oxygen therapy (HBOT; 1 review)

Bennett 2004 evaluated the efficacy and safety of HBOT in pwMS (9 RCTs, 504 participants). The initial treatment course of HBOT consisted of 20 treatment sessions over four weeks; the dose of oxygen per treatment session varied between studies. Two trials produced modest, positive results; however, these were isolated, and difficult to ascribe biological plausibility. There was some improvement in the mean EDSS score at 12 months in the HBOT group (group mean reduction in EDSS compared to sham -0.85 of a point, 95% CI -1.28 to -0.42; $P = 0.0001$). Seven trials reported no evidence of a general treatment effect. There was inconsistent evidence of benefit for the secondary outcomes, such as fatigue, pyramidal system function, and sphincter function. Overall findings

suggested that there was no consistent evidence to confirm a beneficial effect of HBOT in pwMS.

Whole-body vibration (WBV; 1 review)

Sitjå Rabert 2012 examined the efficacy of WBV on functional performance in persons with neurodegenerative diseases, including MS. Of 10 RCTs identified, 4 RCTs, with 64 participants, were conducted in the MS population. The included trials used different vibration parameters (range from 2 to 26 Hz) and different vibration platform types (rotational platform, platform that generates vertical sinusoidal displacements, or random platform). The authors found no evidence of a short-term or long-term effect of WBV on any functional outcomes (body balance, gait, muscle performance) or QoL, compared with other active physical therapy or passive interventions.

Occupational therapy (1 review)

Steultjens 2003 evaluated the efficacy of occupational therapy (OT) on functional outcomes, and social participation, health-related QoL, or both, in pwMS. The authors found three trials (1 RCT and 2 CCTs, 274 participants). The OT approach evaluated a group energy conservation course (2 trials) and counselling intervention. The review authors found inconclusive evidence for any OT interventions in pwMS. Two included trials (both CCTs) reported a beneficial effect of energy conservation group therapy, however, the evidence was insufficient, due to methodological flaws.

Cognitive and psychological interventions (3 reviews)

Rosti-Otajärvi 2014 assessed the effects of neuropsychological, cognitive rehabilitation on cognitive performance and emotional well-being in pwMS (20 RCTs, 986 participants). The review authors reported that cognitive training improved memory span (SMD 0.54, 95% CI 0.20 to 0.88; $P = 0.002$), and working memory (SMD 0.33, 95% CI 0.09 to 0.57; $P = 0.006$). Cognitive training combined with other neuropsychological rehabilitation methods also improved attention (SMD 0.15, 95% CI 0.01 to 0.28; $P = 0.03$), immediate verbal memory (SMD 0.31, 95% CI 0.08 to 0.54; $P = 0.008$), and delayed memory (SMD 0.22, 95% CI 0.02 to 0.42; $P = 0.03$). No improvement was found for emotional function. The overall quality of the included studies was low, due to methodological limitations and heterogeneity of interventions and outcome measures. The review authors concluded there was low-quality evidence suggesting that neuropsychological rehabilitation improved cognitive functions (improved memory span, working memory, attention), but none for emotional function.

Thomas 2006 evaluated the effectiveness of psychological interventions, including cognitive behavioural therapy (CBT), in pwMS (16 RCTs, 1006 participants). CBT was found to be beneficial in the treatment of depression, and in helping people adjust to, and cope with, having MS. The authors were unable to interpret results conclusively, due to the range of outcome measures used, and heterogeneity amongst the trials. Psychological interventions were diverse in nature; CBT was the most frequently used approach. None of the studies focused on psychological approaches to managing common symptoms of MS, such as fatigue and pain. The majority of the included studies had various methodological flaws, including small sample size, lack of proper randomisation and allocation concealment methods, and lacked a clear description of withdrawals.

das Nair 2016 evaluated the effectiveness of memory rehabilitation on memory functions and functional abilities in a subgroup of pwMS with memory problems, compared to those who were given no treatment, or received a placebo. The review authors included 15 RCTs, with a total of 989 participants, which evaluated a wide range of memory retraining techniques, such as computerised programmes, and internal and external memory aids. The findings suggested a significant effect of the interventions on objective assessments of memory at both the immediate- (SMD 0.23, 95% CI 0.05 to 0.41), and long-term follow-up (SMD 0.26, 95% CI 0.03 to 0.49), and on QoL in the immediate-term follow-up (SMD 0.23, 95% CI 0.05 to 0.41). The intervention group performed significantly better than the control group in ADLs at long-term follow-up (SMD -0.33, 95% CI -0.63 to -0.03). There was no significant effect on subjective reports of memory problems at short-term (SMD 0.04, 95% CI -0.19 to 0.27), or long-term follow-up (SMD 0.04, 95% CI -0.19 to 0.27); on mood at short-term (SMD 0.02, 95% CI -0.16 to 0.20), or long-term follow-up (SMD -0.01, 95% CI -0.21 to 0.20); at short-term follow-up for ADL (SMD -0.13, 95% CI -0.60 to 0.33); or at long-term follow-up for QoL (SMD 0.16, 95% CI -0.03 to 0.36). The authors concluded that there was low-quality evidence suggesting that memory rehabilitation techniques may improve memory function and QoL.

Nutritional and dietary supplement intervention (2 reviews)

Farinotti 2012 evaluated the efficacy and safety of dietary regimens for pwMS (6 RCTs, 794 participants). These studies evaluated different form of polyunsaturated fatty acids, given for 12 to 30 months, including omega-6 fatty acids (N-6 PUFA) – linoleic acid, or omega-3 fatty acids (N-3 PUFA) – fish oil. The review authors reported that polyunsaturated fatty acids did not have significant effects on clinical outcomes in MS (disease progression). Similarly, they found that omega-6 fatty acids and linoleic acid had no beneficial effects. There were inconclusive data on safety.

Jagannath 2010 assessed the safety and effectiveness of vitamin D in the management of MS. The authors found only one RCT conducted over 52 weeks, which treated 25 patients with escalating doses of vitamin D compared with controls (N = 24). Participants in the intervention group received 40,000 IU/day over 28 weeks to raise serum 25-hydroxyvitamin D (25(OH)D) rapidly, followed by 10,000 IU/day for 12 weeks; they were then down-titrated to 0 IU/day. The control group received a regular dose (4000 IU/day) of vitamin D. There was limited evidence that escalating doses of vitamin D might improve relapse rates, disability scores, and suppression of T-cell proliferation. Vitamin D was safe, with no adverse effects. However, the study was of low quality, with a potential high risk of bias, which limited the generalisability of the findings.

Vocational rehabilitation (1 review)

Khan 2009 examined the effectiveness of vocational rehabilitation programmes compared to alternative programmes or usual care on return to work, work ability, and employment in pwMS. The authors only found two poor quality trials (1 RCT and 1 CCT, 80 participants). The evidence was inconclusive for the effects of specific vocational interventions on outcomes, such as: competitive employment, altering rates of job retention, changes in employment, rates of re-entry into labour force, altering work ability, employability maturity, or job-seeking activity. The authors highlighted the need for clinicians to be aware of vocational issues,

to incorporate practical solutions to deal with work disability, and workplace accommodation, and to educate employers and the wider community to understand and manage barriers for maintaining employment.

Information-provision interventions (1 review)

Kopke 2014 evaluated the effectiveness of information-provision interventions for pwMS, to promote informed choices and improve patient-relevant outcomes. The authors found 10 RCTs (1314 participants), which included interventions providing disease-specific information, such as information leaflets, booklets, manuals or pamphlets, educational programmes or lectures, audio-visual aids, like videos, tape recordings, computer programmes or websites, web systems, including podcasts, social networks or other information technologies (smartphones, decision-support tools), or personal information (e.g. house visits or telephone calls). The authors reported moderate-quality evidence for MS-related knowledge delivery programmes (N = 4 RCTs, 524 participants) in successfully increasing participants' knowledge. There were mixed results and low-quality evidence from studies reporting effects on decision-making (N = 4 RCTs, 836 participants), and from studies assessing QoL (N = 5 RCTs, 605 participants). The authors concluded that providing information to pwMS seemed to increase disease-related knowledge, with less clear results on decision making and QoL.

Other reviews on specific rehabilitation interventions

Telerehabilitation (1 review)

Khan 2015 examined the effectiveness and safety of telerehabilitation intervention in pwMS (9 RCTs, 531 participants). These studies evaluated various telerehabilitation interventions with more than one rehabilitation component, and predominantly included physical activity, educational, behavioural, and symptom-management programmes. There was low-quality evidence for any form of telerehabilitation interventions in reducing short-term disability, impairments (such as fatigue, pain, insomnia); or in improving functional activities, psychological outcomes, or QoL in the longer term. There were no data on cost-effectiveness or process evaluation (participants' and therapists' satisfaction). Despite the lack of high-quality evidence, the authors concluded that a range of telerehabilitation interventions could be an alternative efficient and cost-effective method to deliver rehabilitation treatment in a setting convenient to the patient, and in remote areas where there were limited rehabilitation services.

Interventions for the management of spasticity (1 review)

Amatya 2013 evaluated non-pharmacological interventions for treating spasticity in pwMS. The authors included 9 RCTs, with 341 participants, which evaluated a wide range of non-pharmacological interventions: physical activity programmes (such as physiotherapy, structured exercise programmes, sports climbing), transcranial magnetic stimulation (intermittent theta burst stimulation (iTBS), repetitive transcranial magnetic stimulation (rTMS)), electromagnetic therapy, transcutaneous electrical nerve stimulation (TENS); and whole body vibration. The authors reported low-quality evidence that physical activity programmes used in isolation, or in combination with other interventions (pharmacological or non-pharmacological), and for magnetic stimulation (iTBS, rTMS), with or without adjuvant exercise therapy may improve spasticity in pwMS. There was no

evidence to support the use of TENS, sports climbing, or vibration therapy for treating spasticity in this population.

DISCUSSION

Summary of main results

This review systematically summarised the best, up-to-date evidence from published Cochrane Reviews for the effectiveness of rehabilitation interventions in people with multiple sclerosis (pwMS). Rehabilitation is considered to be a key supportive treatment in MS. A range of rehabilitative approaches have been evaluated in this population. However, findings indicate that evidence to support the use of various interventions is relatively poor. There is a lack of high-quality evidence for the effectiveness of various modalities, due to the limited number of methodologically robust studies. The key findings of this review, based on outcomes according the International Classification Functioning, Disability and Health (ICF) framework that focus on the following categories, are outlined in [Table 2](#), and summarised below:

Function

- Moderate-quality evidence that inpatient or outpatient multidisciplinary rehabilitation programmes improved functional activities and bladder related activity.
- Moderate-quality evidence that physical therapeutic modalities (exercise, physical activities) improved functional outcomes (mobility, muscular strength).
- Low-quality evidence that exercise therapy may improve balance.
- Low-quality evidence that whole body vibration may improve any functional outcomes (balance, gait, muscle performance), or QoL.
- Low-quality evidence that telerehabilitation may reduce short-term disability and improve functional activities.

Impairments

- Moderate-quality evidence that physical therapeutic modalities (exercise, physical activities) reduced patient-reported fatigue.
- Low-quality evidence that multidisciplinary rehabilitation (outpatient and home-based) programmes might provide short-term improvements in symptoms.
- Low-quality evidence that specific therapy programmes targeting MS-related spasticity may improve spasticity.
- Low-quality evidence that telerehabilitation may reduce symptoms (such as fatigue, pain, insomnia).

Participation

- Moderate-quality evidence that inpatient or outpatient multidisciplinary rehabilitation programmes improved participation outcomes (such as QoL) up to 12 months.
- Moderate-quality evidence that information provision increased patient's knowledge.
- Moderate-quality evidence that exercise therapy improved psychological symptoms (such as mood) and QoL.
- Low-quality evidence that neuropsychological interventions may improve memory span, working memory, and attention.

- Low-quality evidence that cognitive behavioural therapy may improve depression, adjustment, and the ability to cope with MS.
- Low-quality evidence that memory rehabilitation programmes may improve memory immediately, and in the long-term.
- Low-quality evidence that whole body vibration may improve QoL.
- Low-quality evidence that vocational rehabilitation may improve competitive employment, job retention, changes in employment, rates of re-entry into the labour force; work ability by improving participants' confidence in the accommodation request process, employability maturity, or job seeking activity.
- Low-quality evidence for telerehabilitation may improve QoL and psychological outcomes.

Synthesis of best evidence from this review, based on type of rehabilitation interventions, suggest there was:

Moderate-quality evidence for:

- Inpatient or outpatient multidisciplinary rehabilitation programmes to improve disability, bladder related activity, and participation outcomes up to 12 months.
- Physical therapeutic modalities (exercise, physical activities) to improve functional outcomes (mobility, muscular strength) and QoL, reduce patient-reported fatigue.
- Information provision to increase patient's knowledge.
- Exercise therapy to improve psychological symptoms (such as mood).

Low-quality evidence for:

- Multidisciplinary rehabilitation (outpatient and home-bases) programmes that may improve symptoms and disability in the short term.
- Exercise therapy that may improve balance and symptoms.
- Neuropsychological interventions that may improve memory span, working memory, and attention.
- Cognitive behavioural therapy that may improve depression, adjustment, and the ability to cope with MS.
- Memory rehabilitation programmes that may improve memory or functional abilities, immediately or in the long term.
- Whole body vibration that may improve any functional outcomes (balance, gait, muscle performance), or QoL.
- Specific therapy programmes targeting MS-related spasticity that may improve spasticity.
- Vocational rehabilitation that may improve competitive employment, job retention, changes in employment, rates of re-entry into the labour force; work ability by improving participants' confidence in the accommodation request process, employability maturity, or job seeking activity.
- Telerehabilitation that may reduce short-term disability, improve functional activities, impairments (such as fatigue, pain, insomnia), QoL, and psychological outcomes.

Inconclusive evidence for:

- Occupational therapy strategies on functional ability, social participation, QoL, or a combination.
- Hyperbaric oxygen therapy on any patient outcomes.

- Neuropsychological interventions on emotional function.
- Dietary interventions (polyunsaturated fatty acids, vitamin D) on clinical outcomes.

Overall completeness and applicability of evidence

This overview of Cochrane Reviews investigating the effectiveness of rehabilitation interventions in pwMS found a large degree of variation in interventions, outcome measurement tools, control protocols, and length of follow-up. Due to this heterogeneity, we were unable to pool data in meta-analyses, and were only able to conduct best-evidence syntheses using qualitative analyses. The identified heterogeneity may also reflect the wide variety of rehabilitation interventions, conducted in different settings, under different healthcare systems, with patients with varied severity and stages of MS. This review only included published Cochrane Reviews. The authors acknowledge that the overall summary reported in this review cannot be regarded as the best and most inclusive findings, as we excluded many published, relevant non-Cochrane reviews in this area ([Andreassen 2011](#); [Asano 2014](#); [Bilkman 2013](#); [Bronson 2010](#); [Campbell 2016](#); [Cruickshank 2015](#); [Dalgas 2015](#); [Glinsky 2007](#); [Haselkorn 2015](#); [Kalron 2015](#); [Kantele 2015](#); [Kjohede 2012](#); [Latimer-Cheung 2013](#); [Mitolo 2015](#); [Paltamaa 2012](#); [Snook 2009](#); [Yu 2014](#); [Yu 2014a](#)). However, the non-Cochrane reviews varied in scope and methodology, and lacked a standardised reporting protocol, which resulted in diverse conclusions. Therefore, we believe that including only Cochrane Reviews in this overview, potentially provided the least biased estimate of the impact of rehabilitation interventions in pwMS. It also provided reassurance about whether or not the conclusions of individual reviews were consistent ([Smith 2011](#)).

Despite strong recommendations to update Cochrane Reviews every two years, it was more than two years since the majority of the included reviews were last published or updated. Of the 15 included reviews, only one review included evidence up to June 2015 ([das Nair 2016](#)). Four included reviews could be considered out of date, as these reviews only included evidence published prior to 2010, implying that recent trials may have been missed ([Jagannath 2010](#); [Rietberg 2005](#); [Steultjens 2003](#); [Thomas 2006](#)). For the rest of the reviews, the literature search date had already exceeded two years, so technically, they would also be considered out of date.

Rehabilitation for pwMS should include a wide spectrum of treatment, and use different interventions, which need to be individualised, because of the diverse clinical presentations, varying levels of disability, and changing needs of these individuals ([Khan 2010](#)). This reflects the wide variety of rehabilitation interventions included in this review. However, we found that many of the evaluated interventions were broadly described; specifically exercise interventions (aerobic, strength, flexibility, mobility, range of motion, postural control and balance training, bicycle, ergometry, etc. ([Rietberg 2005](#))), and psychological interventions (cognitive behavioural therapy, psychoanalytic therapy, counselling, psycho-education, computer-based psychological training programmes, memory aids, etc. ([das Nair 2016](#); [Thomas 2006](#))). Sufficient details to enable replication of many of these interventions were lacking, and few studies demonstrated the implementation of their included interventions. Many of these interventions have yet to be included in comprehensive multidisciplinary rehabilitation programmes ([Khan 2007b](#)). Included reviews also failed to provide information

on optimal settings, type, intensity, and duration of therapy, and cost-effectiveness of the rehabilitation interventions.

Rehabilitation interventions are complex and difficult to quantify, and the active ingredient in the intervention is not directly identifiable ([Khan 2015](#)). The majority of the reviews included a study population with all types of MS. The included reviews consistently remarked on the relatively small numbers of patients, with marked heterogeneity of disease type, clinical presentation, and goals for treatment in the primary trials. The majority of review authors also argued that control arms, specifically those that used 'usual care', were poorly described across the primary trials. There was also a marked heterogeneity amongst the outcome measures used, even to evaluate similar functional or psychological outcomes, and assessment time points in the primary trials. This was reflected in the challenges encountered in assimilating, or pooling the data in meta-analyses, or both. Therefore, the quality of the overall evidence for many of the rehabilitation interventions, and external validity of the findings, should be interpreted cautiously.

Quality of the evidence

We assessed that all included reviews were of high to moderate quality, however, many were not recently published or updated. The quality of the evidence supporting the findings was limited by the small number of primary studies, and methodological limitations of these trials within the included reviews. The main sources of bias in the primary studies were methodological limitations, such as inadequate or lack of blinding of participants and outcome assessors, and inadequate reporting of allocation concealment and randomisation methods. There were also inconsistencies and heterogeneity in the outcome measures, and assessment and follow-up periods. Many studies included relatively small numbers of participants (statistically underpowered), and there was a marked heterogeneity in disease types and clinical presentation of the participants, and goals for treatment. We could not rule out some degree of selection, publication, and reference bias from the literature searches in the included reviews.

Potential biases in the overview process

Overall, data from the included Cochrane Reviews did not provide clinically relevant evidence for the majority of rehabilitation interventions of interest. This might be due to several limitations in the review process. We only included currently published Cochrane Reviews. Although these reviews strictly followed the Cochrane guidelines, and adopted a thorough search strategy, many were not updated; therefore, there is a strong likelihood there were missing relevant articles published beyond the search date of the included reviews. Four included reviews were conducted by the present authors' team ([Amatya 2013](#); [Khan 2007b](#); [Khan 2009](#); [Khan 2015](#)), and one author (FK) was involved in another review ([Kopke 2014](#)). Independence of assessors' judgment evaluating these reviews cannot be confirmed. However, as Cochrane sets the standards for research synthesis, and as we independently followed a strict, standard appraisal protocol for all included reviews, and resolved disagreement by consensus among all review authors, we think this might have minimal impact on the overall quality assessment process. The majority of the reviews only searched for papers published in English, hence, there was a likelihood of missing data available in other languages.

Agreements and disagreements with other studies or reviews

[Haselkorn 2015](#) conducted a systematic review that provided an overview of the evidence for physical rehabilitation for pwMS. In contrast to this overview review, the authors included 142 individual trials (all designs; published between 1970 and 2013), rated the evidence using American Academy of Neurology criteria, and focused specifically on individual trials of physical therapies. However, this present overview used a global approach to scrutinise the MS literature, by evaluating all published Cochrane Reviews that explored a broad range of rehabilitation modalities, and using globally-endorsed appraisal methodology (AMSTAR and GRADE).

[Bennett 2010](#) conducted a narrative review to present evidence for a specific type of exercise to control MS symptoms and improve functional recovery, but did not provide a systematic approach to the evaluation of the evidence.

Both of these reviews varied in quality, scope, and methodology, with diverse findings.

Most recently, two authors (BA, FK) systematically evaluated the evidence from published systematic reviews of clinical trials on the effectiveness of rehabilitation to improve function and participation in pwMS ([Khan 2017](#)). This overview included both Cochrane and non-Cochrane reviews, published up to 31 January 2016. Given that [Khan 2017](#) included all the Cochrane Reviews that we included in this overview, there is considerable overlap in the findings and conclusions. Similar to [Khan 2017](#) and [Haselkorn 2015](#), we found that inpatient and outpatient physical therapy, and comprehensive multidisciplinary rehabilitation, improved function and disability in pwMS. However, in contrast to the previous reviews, we found only moderate-quality evidence supporting physical therapy for pwMS. This discrepancy is likely due to the stringent methodological approach we followed for this review, and the different inclusion criteria among the reviews.

AUTHORS' CONCLUSIONS

Implications for practice

Multiple sclerosis (MS) is a complex condition, which frequently presents with multiple deficits (motor, sensory, cognitive, behavioural, and communication issues) that require tailored and co-ordinated, longer-term, multidisciplinary rehabilitative care. The evidence presented in this overview of Cochrane Reviews supports the strategy that recommends varied approaches to rehabilitation. The type and setting of the rehabilitation treatment (inpatient, community) should be individualised, based on a patient's specific needs. The evidence showed that although there was a broad range of rehabilitative treatments available to treat people with MS (pwMS), there was a critical lack of high-quality evidence showing the effectiveness of various modalities. Gaps in this knowledge could be used to set directions for future research.

The literature most commonly examined the effects of different forms of physical therapeutic modalities and neuropsychological interventions in this population. Physical therapeutic modalities (exercise or physical activities) improved functional outcomes (mobility, muscle strength, aerobic capacity) and quality of life (QoL), and reduced patient-reported fatigue. A comprehensive multidisciplinary rehabilitation approach showed longer-term gains in activity (disability) and participation. However, readers should interpret the evidence for many of the rehabilitation interventions cautiously, as the majority of the included reviews found only moderate-quality evidence, and did not include the most current studies. The evaluated rehabilitation interventions were considered safe; however, many studies did not report adverse effects.

Implications for research

People with MS require specialised, flexible services for comprehensive management. In line with escalating healthcare costs, and the increased demand for rehabilitation services for pwMS, it is important to justify the expense of rehabilitation services. This overview highlights the limitations of studies in rehabilitation settings, and the need for more methodologically robust trials to build a strong evidence base in this area. Many primary trials in the included reviews tended to be of modest sample size, used a range of outcome measures, and did not always adhere to the CONSORT guidelines ([das Nair 2016](#); [Moher 2001](#)). This limited the true picture from these studies, making it difficult to collate data for meta-analyses, and to allow informed decisions about the fidelity of the authors' conclusions ([das Nair 2016](#)). Other specific guidance, such as the intervention description and replication (TIDieR) checklist and guide may help to improve the quality of the reporting of trials of complex rehabilitation interventions ([Hoffman 2014](#)). The patients' and caregivers' perspective should be incorporated, and associated costs or economic benefit of interventions should be further explored. Participation issues relevant to MS (social reintegration, psychosocial issues, and recreational or vocational issues) need further evaluation. There is an increasing awareness of the contribution of rehabilitation in early and long-term MS care. Further research is needed to build evidence for different components, modalities, duration of rehabilitation treatments, and for interventions that can be integrated into a comprehensive, multidisciplinary, rehabilitation programme.

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ADDITIONAL TABLES

Table 1. Characteristics of included reviews

Author and Year	Date assessed as up to date	Population	Intervention	Comparison interventions	Outcomes for which data were reported	Meta-analysis	Review limitations	R-AMSTR score*
Amatya 2013	1996 to June 2012	N = 9 RCTs, 341 participants with all types of MS	Non-pharmacological spasticity management interventions	Sham or placebo interventions; lower level or different types of intervention; minimal intervention; waiting-list controls or no treatment; interventions given in different settings	Primary Reduction in spasticity; improvement in upper limb functioning and (upper limb-related) ADL; improvement in mobility Secondary improvement in symptoms or impairments; restriction in participation and impact on caregivers; costs	No	<ul style="list-style-type: none"> Results not pooled Publication bias not assessed using graphic aids and statistical tests Statement of support or conflict of interest in the primary inclusion studies not mentioned 	41
Bennett 2004	up to 25 February 2011	N = 9 RCTs, 504 participants with all types of MS	HBOT	Placebo or no treatment	Primary Disability status, objective assessment; suffering ≥ 1 exacerbation at 6 to 12 months; side effects Secondary Functional scores assessed by neurologists	Yes	<ul style="list-style-type: none"> Grey literature not searched Non-English language publication not included Statement of support or conflict of interest in the primary inclusion studies not mentioned 	41
das Nair 2016	up to June 2015	N = 15 RCTs, 989 participants with all types of MS	Memory rehabilitation	No treatment or placebo	Primary Subjective and objective reports of memory Secondary Mood, functional abilities, QoL	Yes	<ul style="list-style-type: none"> Manual search of relevant journals not conducted Statement of support or conflict of interest in the primary inclusion studies not mentioned 	42
Farinotti 2012	up to November 2011	N = 6 RCTs, 794 participants with	Dietary intervention (polyunsaturated fatty	No dietary modification or placebo	Primary Disability progression; exacerbation during study period	No	<ul style="list-style-type: none"> Results not pooled Grey literature and manual search of rele- 	42

Table 1. Characteristics of included reviews (Continued)

		all types of MS	acids, vita- mins)		Secondary				
					HRQoL; cognitive functio; physical and psychological functions; safety (adverse events)				vant journals not con- ducted <ul style="list-style-type: none"> • Publication bias not as- sessed using graphic aids and statistical tests • Statement of support or conflict of interest in the primary inclusion studies not mentioned
Heine 2015	1966 to Oc- tober 2014	N = 45 RCTs, 2250 partic- ipants with all type of MS	Exercise therapy (fa- tigue)	Non-exercise control or an- other inter- vention	Primary Fatigue Secondary Safety, relapses	Yes			40 <ul style="list-style-type: none"> • Grey literature and manual search of rele- vant journals not con- ducted • Statement of support or conflict of interest in the primary inclusion studies not mentioned
Jagannath 2010	up to 17 May 2010	N = 1 RCTs, 49 partici- pants with all types of MS	Dietary in- tervention (vitamin D)	Placebo or no supplementa- tion	Primary Number of relapses; time-to- first treated relapse; QoL; dis- ability status; safety and ad- verse effects Secondary Hospitalisation; cognitive functions; physical symp- toms; psychological symp- toms; change in MRI parame- ters; serum levels of 25-hy- droxyvitamin D (25(OH)D); vi- tamin D & calcium; bone min- eral density (BMD); cytokine profile; T lymphocyte prolifer- ation response & plasma met- alloprotease-9 activity	No			40 <ul style="list-style-type: none"> • Results not pooled • Grey literature and manual search of rele- vant journals not con- ducted • Statement of support or conflict of interest in the primary inclusion studies not mentioned
Khan 2007b	up to 25 February 2011 (up- dated)	N = 9 RCTs & 1 CCT, 954 participants with mod- erate to se-	Multidisci- plinary re- habilitation	Lower level or different types of in- terventions; intervention	Primary Minimisation of disability (limitation in activity) Secondary	No			40 <ul style="list-style-type: none"> • Results not pooled • Publication bias not as- sessed using graphic aids and statistical tests

Table 1. Characteristics of included reviews (Continued)

		vere disabil- ities		given in differ- ent settings; lower intensi- ty of interven- tion	Participatory issues, such as QoL, psychological adjust- ment; cost; service utilisation; and care burden		<ul style="list-style-type: none"> statement of support or conflict of interest in the primary inclusion studies not mentioned 	
Khan 2009	1981 to Feb- ruary 2011	N = 1 RCT & 1 CCT, 80 MS participants of working age (mean age 18 to 65 years)	Vocational rehabilita- tion	Alternative programmes or care as usu- al	Primary Competitive employment; supported employment Secondary Return to work; disability pension; work ability; costs	No	<ul style="list-style-type: none"> Results not pooled Grey literature and manual search of rele- vant journals not con- ducted Publication bias not as- sessed using graphic aids and statistical tests Statement of support or conflict of interest in the primary inclusion studies not mentioned 	40
Khan 2015	up to 9 July 2014	N = 9 RCTs, 531 partici- pants, (469 included in analyses); majority RRMS	Telerehabili- tation	Lower level or different types of in- tervention; minimal in- tervention; waiting-list controls or no treatment (or usual care); interventions given in differ- ent settings	Primary Improvement in functional activity (ADLs, mobility, con- tinence, etc.); symptoms or impairments (pain, spasm fre- quency, joint range of move- ment, involuntary move- ments, spasticity, etc.); par- ticipation and environmen- tal, personal context, or both (QoL, psychosocial function, employment, education, so- cial and vocational activities, patient and caregiver mood, relationships, social integra- tion, etc.) Secondary Compliance; service utilisa- tion and cost; adverse events	No	<ul style="list-style-type: none"> Results not pooled Publication bias not as- sessed using graphic aids Statement of support or conflict of interest in the primary inclusion studies not mentioned 	42
Kopke 2014	up to 12 June 2013	N = 10 RCTs, 1314 partic- ipants with	Information provision that aims	Usual care or other types of informa-	Primary	No	<ul style="list-style-type: none"> Results not pooled 	38

Table 1. Characteristics of included reviews (Continued)

		all types of MS	to promote informed choice and improve patient outcomes	tion-provision interventions	Disease-related (risk) knowledge; measures of (shared) decision making			<ul style="list-style-type: none"> Grey literature and manual search not conducted Homogeneity not assessed to pooled the data Statement of support or conflict of interest in the primary inclusion studies not mentioned
					Secondary QoL; informed choice; psychological status; treatment choices; treatment compliance; satisfaction with information received, decisional process; hospital admissions and use of healthcare services; ADLs; coping; disability; role preferences; adverse events			
Rietberg 2005	1966 to March 2004	N = 9 RCTs, 260 participants with low to moderate disabilities	Physical (exercise) therapy	Control interventions (details not provided)	Primary Activities limitation; HRQoL Secondary None	No	<ul style="list-style-type: none"> Results not pooled Grey literature and manual search of relevant journals not conducted Homogeneity not assessed to pooled the data Publication bias not assessed using graphic aids and statistical tests statement of support or conflict of interest in the primary inclusion studies not mentioned 	35
Rosti-Otajarvi 2014	up to 28 May 2013	N = 20 RCTs, 986 participants with all types of MS	Neuropsychological rehabilitation	Other interventions or no intervention	Primary Measures of cognitive function Secondary Depression; fatigue; personality disturbance; anxiety; QoL; return to work; activity level	Yes	<ul style="list-style-type: none"> Grey literature and manual search of relevant journals not conducted Statement of support or conflict of interest in the primary inclusion studies not mentioned 	42
Sitja Rabert 2012	1964 to 6 May 2011	N = 4 RCTs, 64 participants	WBV	Passive intervention	Primary	Yes	<ul style="list-style-type: none"> Grey literature and manual search of relevant journals not conducted 	39

Table 1. Characteristics of included reviews (Continued)

		pants with all types of MS		(waiting list, non-treatment, usual lifestyle); any other active physical therapy intervention (balance programme, walking, resistance training, etc.); another WBV under different vibration parameters.	Functional performance according to basic ADL		vant journals not conducted <ul style="list-style-type: none"> • Publication bias not assessed using graphic aids and statistical tests • Statement of support or conflict of interest in the primary inclusion studies not mentioned 	
Steultjens 2003	up to January 2003	N = 1 RCT & 2 CCTs, 274 participants with all types of MS	OT	Control interventions (details not provided)	Primary Fatigue; pain; functional ability; social participation; QoL Secondary Knowledge about disease management; self-efficacy; motor co-ordination and balance	No	<ul style="list-style-type: none"> • Results not pooled • Grey literature and manual search of relevant journals, bibliographies not conducted • Homogeneity not assessed to pooled the data • Publication bias not assessed using graphic aids and statistical tests • Statement of support or conflict of interest in the primary inclusion studies not mentioned 	34
Thomas 2006	up to December 2004	N = 16 RCTs, 1006 participants with all types of MS	Cognitive rehabilitation	Usual care or standard care; placebo; waiting-list controls; other psychological interventions; other interventions	Primary Disease-specific and general QoL; psychiatric symptoms; psychological functioning; disability; cognitive outcomes Secondary Number of relapses; pain; fatigue; healthcare utilisation;	Yes	<ul style="list-style-type: none"> • Publication bias not assessed using graphic aids and statistical tests • Statement of support or conflict of interest in the primary inclusion studies not mentioned 	41

Table 1. Characteristics of included reviews *(Continued)*

changes in medication; adherence to other therapies

ADL = activities of daily living; CBT = cognitive behavioural therapy; CCT = clinical controlled trial; HBOT = hyperbaric oxygen therapy; HRQoL = health-related quality of life; ICF = International Classification Functioning, Disability and Health; MS = multiple sclerosis; OT = occupational therapy; PD = Parkinson's disease; PT = physical therapy; QoL = quality of life; RCT = randomised controlled trial; WBV = whole body vibration

*R-AMSTAR = Revised Assessment of Multiple Systematic Reviews (Total score out of 44; details in: [Appendix 2](#); [Appendix 3](#))

Table 2. Summary of findings from included reviews

Rehabilitation interventions for people with multiple sclerosis (pwMS)					
Outcome*	Intervention and Comparison intervention	Illustrative comparative risks (95% CI)		Number of participants (studies)	Quality of the evidence (GRADE)**
		Assumed risk	Corresponding risk		
		With comparator	With intervention		
Function (mobility, ADLs)	Intervention: Multidisciplinary rehabilitation (MD) - inpatient Comparison: Lower level or different types of interventions; intervention given in different settings; lower intensity of intervention.	There was evidence that inpatient MD rehabilitation can improve functional independence, mobility and locomotion (wheelchair users only)		217 participants (3 RCTs)	⊕⊕⊕⊖ Moderate ¹
	Intervention: Multidisciplinary rehabilitation (MD) - inpatient or outpatient Comparison: Lower level or different types of interventions; intervention given in different settings; lower intensity of intervention.	There was evidence that an inpatient or outpatient MD rehabilitation program can improve function and bladder impairment		101 participants (1 RCT)	⊕⊕⊕⊖ Moderate ²
	Intervention: Exercise Comparison: Control interventions (details not provided)	There was evidence that exercise therapy can improve muscle power, function, exercise tolerance, and mobility-related activities more than no exercise.		260 participants (9 RCTs)	⊕⊕⊕⊖ Moderate ¹
	Intervention: Whole-body vibration Comparison: Passive intervention; any other active physical therapy intervention; another vibration therapy under different vibration parameters	The mean body balance ranged across control groups from 242 to 245 mm	The mean body balance in the intervention groups was 19.83 higher (20.99 lower to 60.65 higher)	64 participants (4 RCTs)	⊕⊕⊖⊖ Low ³
	Intervention: Telerehabilitation programme Comparison: Lower level or different types of intervention; minimal intervention; waiting-list controls or no treatment (or usual	There was evidence that a telerehabilitation programme may improve functional activities, such as physical activity, walking, balance capacity, and postural control for the short-term (up to 3 months)		45 participants (1 RCT)	⊕⊕⊖⊖ Low ⁴

Table 2. Summary of findings from included reviews (Continued)

care); interventions given in different settings

Impairments (symp-toms)	Intervention: Various non-pharmacological spasticity management interventions Comparison: Sham or placebo interventions; lower level or different types of intervention; minimal intervention; waiting-list controls or no treatment; interventions given in different settings	<p>There was evidence that addition of active physiotherapy after BoNT injection may reduce spasticity up to 12 weeks: MAS score at week 2 (2.73 versus 3.22 in control), at week 4 (2.64 versus 3.33 in control), and at week 12 (2.68 versus 3.33 in control); $P < 0.01$ for all time points.</p> <p>There was evidence that iTBS alone or in combination with exercise therapy may reduce spasticity after 2 weeks: MAS scores in the stimulated leg (2.1 ± 0.4 before treatment; 1.3 ± 0.4 after treatment; $P < 0.05$), MSSS-88 (74.3 ± 11.4 before treatment; 53.2 ± 10.9 after treatment; $P < 0.001$), FSS (39.5 ± 4.2 before treatment; 31.6 ± 4.6 after treatment; $P < 0.05$).</p> <p>There was evidence that rTMS may reduce spasticity (MAS score; mean change -3.3 ± 4.7 AU versus 0.7 ± 2.5 AU in control group; $P = 0.003$).</p> <p>There was evidence that pulsed electromagnetic therapy may reduce spasticity ($P < 0.005$) and fatigue ($P = 0.04$).</p> <p>There was evidence that magnetic pulsing device may improve a performance scale (PS) combined rating for bladder control, cognitive function, fatigue level, mobility, spasticity, and vision (change in PS scale -3.83 ± 1.08 versus -0.17 ± 1.07 in control group, $P < 0.005$).</p>	341 participants (9 RCTs)	⊕⊕⊕⊕ Low ³	Data were not pooled in this review due to various interventions and use of different outcome measures
	Intervention: HBOT Comparison: Placebo or no treatment	<p>There was evidence that HBOT may reduce mean EDSS at 12 months (group mean reduction in EDSS compared to sham -0.85, $P = 0.0001$).</p>	504 participants (9 RCTs)	⊕⊕⊕⊕ Low ³	Data from only 2 RCTs showed some benefits and majority of trials (7 RCTs) reported no evidence
	Intervention: Different exercise therapy: endurance training (23 interventions), muscle power training (9 interventions), task-oriented training (5 interventions), mixed training (15 interventions), or other (e.g. yoga (17 interventions))	<p>There was evidence that overall, exercise therapy can reduce fatigue (SMD -0.53; $P < 0.01$).</p> <p>There was evidence that different types of exercise therapy can reduce fatigue: endurance training (SMD -0.43; $P < 0.01$), mixed training (SMD -0.73; $P < 0.01$), and other training, e.g. yoga (SMD -0.54; $P < 0.01$)</p>	2250 participants (45 RCTs)	⊕⊕⊕⊕ Moderate ⁵	There was significant heterogeneity between trials due to variability in type, duration, intensity, and use of outcome measures.

Table 2. Summary of findings from included reviews (Continued)

Comparison: Non-exercise control or another intervention					
	Intervention: Telerehabilitation program	There was evidence that a telerehabilitation programme can reduce or improve impairments, such as fatigue in the short term (up to 3 months) and long term; and improved symptoms, such as pain and insomnia in the long term.	489 participants (4 RCTs)	⊕⊕⊕⊖ Low ¹	Data were not pooled in this review due to various interventions and use of different outcome measures.
	Comparison: Lower level or different types of intervention; minimal intervention; waiting-list controls, no treatment, or usual care; interventions given in different settings				
Participation (quality of life, psychological outcomes, vocational and social activities)	Intervention: Exercise	There was evidence that exercise therapy can improve mood more than no exercise.	260 participants (9 RCTs)	⊕⊕⊕⊖ Moderate ¹	Data were not pooled in this review due to variation in outcome measures
	Comparison: Control interventions (details not provided)				
	Intervention: Memory rehabilitation	There was evidence that memory rehabilitation may show improvement in objective assessments of memory in both immediate follow-up (SMD 0.23, 95% CI 0.05 to 0.41) and long-term (3 to 8 months) follow-up (SMD 0.26, 95% CI 0.03 to 0.49)	989 participants (15 RCTs)	⊕⊕⊕⊖ Low ³	The evidence is limited and does not extend to subjective reports of memory functioning or mood. Objective measures used were not valid, potentially limiting generalisability of findings.
	Comparison: No treatment or placebo	There was evidence that memory rehabilitation may improve QoL in the immediate follow-up (SMD 0.23, 95% CI 0.05 to 0.41)			
	Intervention: Neuropsychological rehabilitation	There was evidence that cognitive training may improve memory span (SMD 0.54, 95% CI 0.20 to 0.88; P = 0.002) and working memory (SMD 0.33, 95% CI 0.09 to 0.57; P = 0.006). There was evidence that cognitive training, combined with other neuropsychological rehabilitation methods, might improve attention (SMD 0.15, 95% CI 0.01 to 0.28; P = 0.03), immediate verbal memory (SMD 0.31, 95% CI 0.08 to 0.54; P = 0.008), and delayed memory (SMD 0.22, 95% CI 0.02 to 0.42; P = 0.03).	986 participants (20 RCTs)	⊕⊕⊕⊖ Low ³	Interventions and outcome measures included in the review were heterogeneous, which limited the comparability of the studies
	Comparison: Other interventions or no intervention				
	Intervention: Telerehabilitation program	There was evidence that telerehabilitation programs might improve psychological outcomes and QoL for the long term (> 3 months)	392 (6 RCTs)	⊕⊕⊕⊖ Low ³	Data were not pooled in this review due to various interventions and use of different outcome measures
	Comparison: Lower level or different types of intervention; minimal intervention; waiting-list controls, no treatment, or usual				

Table 2. Summary of findings from included reviews (Continued)

care; interventions given
in different settings

Intervention: Information-provision interventions included: decision aids, educational programmes, self-care interventions, and personal interviews with physicians Comparison: Usual care or other types of information-provision interventions	There was evidence that information provision for patients can improve patients' disease-related knowledge.	524 participants (4 RCTs)	⊕⊕⊕⊖ Moderate ⁶	Data were not pooled in this review due to the marked heterogeneity of the interventions and outcome measures.
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ADL = activities of daily living; BI = Barthel Index; CBT = cognitive behavioural therapy; CCT = clinical controlled trial; CI = confidence interval; EDSS = Expanded Disability Status Scale; HBOT = hyperbaric oxygen therapy; FSS = Fatigue Severity Scale; HRQoL = health-related quality of life; iTBS = intermittent theta burst stimulation; MS = multiple sclerosis; MSQOL-54 = Multiple Sclerosis Quality of Life; MSSS-88 = Multiple Sclerosis Spasticity Scale; OT = occupational therapy; pwMS = persons with multiple sclerosis; PT = physical therapy; PUFAs = polyunsaturated fatty acids; QoL = quality of life; RCT = randomised controlled trial; rTMS = repetitive transcranial magnetic stimulation; SMD = standardised mean difference; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale

*Outcomes categorised according to the International Classification Functioning, Disability and Health (ICF, WHO 2001).

**GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect, and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect, and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Downgraded by one level for imprecision and inconsistency of findings and use of different outcome measures.

²Downgraded by one level due to high risk for imprecision (one single site study).

³Downgraded by two levels for imprecision and inconsistency of findings, due to a number of methodological flaws (high risk of bias in randomisation sequence generation, allocation concealment and blinding) and use of different outcome measures.

⁴Downgraded two levels because the singular study was considered at high risk of bias (unclear risk of bias in randomisation, sequence generation, allocation concealment and blinding of outcome assessors).

⁵Downgraded by one level for imprecision and inconsistency of findings and majority of trials had small sample size and assessed fatigue as a secondary measure.

⁶Downgraded by one level for imprecision and inconsistency of findings, use of different outcome measures and high risk of bias.

APPENDICES

Appendix 1. Key words for the search strategy

Theme 1. Multiple sclerosis

Multiple Sclerosis, Demyelinating Diseases, Transverse myelitis, Optic Neuritis, Acute disseminated encephalomyelitis

Theme 2. Rehabilitation interventions

Rehabilitation, Ambulatory Care, Physical Therapy Modalities, physiotherapy, Exercise therapy, Cognitive therapy, psychotherapy, Behavior/behaviour therapy, Social work, Counselling, Occupational Therapy, Dietetics/Nutrition, Orthotics/brace/orthoses, Acupuncture Patient Care Team, multidisciplinary/ integrated team, cold treatment/cooling, assistive technology device, hydro/pool therapy, Electromagnetic therapy, nerve stimulation, vibration therapy, social participation/support, vocational rehabilitation

MeSH check words

Systematic review/meta-analysis, Review, Adult; Humans

Appendix 2. Quality assessment (R-AMSTAR) of included systematic reviews

R-AMSTAR criteria*	Author year						
	Amatya 2013	Bennett 2004	das Nair 2016	Farinotti 2012	Heine 2015	Jagannath 2010	Khan 2007b
1. Was an a priori design provided?							
A. Clearly focused (PICO-based) question	Y	Y	Y	Y	Y	Y	Y
B. Description of inclusion criteria	Y	Y	Y	Y	Y	Y	Y
C. Study protocol published, registered in advance, or both	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4
2. Was there duplicate study selection and data extraction?							
A. ≥ 2 persons independently extracted the data, explicitly stated	Y	Y	Y	Y	Y	Y	Y
B. Statement of consensus procedure for disagreements	Y	Y	Y	Y	Y	Y	Y
C. Disagreements among extractors resolved properly	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4
3. Was a comprehensive literature search performed?							
A. At least two electronic sources are searched	Y	Y	Y	Y	Y	Y	Y
B. Years & databases used are mentioned	Y	Y	Y	Y	Y	Y	Y
C. Key words, MeSH terms (or both) are stated, and where feasible, the search strategy outline is provided	Y	Y	Y	Y	Y	Y	Y

(Continued)

D. Searches are supplemented by consulting current contents, reviews, textbooks, registers, and by reviewing the references in the studies found	Y	Y	Y	Y	Y	Y	Y
E. Journals are handsearched or manual searched	Y	Y	N	N	Y	N	Y
SCORE	4	4	4	4	4	4	4
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?							
A. Searched for reports regardless of their publication type	Y	Y	Y	N	N	Y	N
B. Any reports based on their publication status, language, etc. excluded	Y	N	Y	N	N	N	N
C. Non-English papers were translated, or readers sufficiently trained in foreign language	N	N	N	N	N	N	N
D. No language restriction or recognition of non-English articles	Y	Y	Y	N	Y	N	Y
SCORE	4	3	4	1	2	2	2
5. Was a list of studies (included and excluded) provided?							
A. Table, list, figure of included studies; a reference list does not suffice	Y	Y	Y	Y	Y	Y	Y
B. Table, list, figure of excluded studies either in the article or in a supplemental source	Y	Y	Y	Y	Y	Y	Y
C. Satisfactory, sufficient statement of the reason for exclusion of the seriously considered studies	Y	Y	Y	Y	Y	Y	Y
D. Reader is able to retrace the included and the excluded studies anywhere in the article bibliography, reference, or supplemental source	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4
6. Were the characteristics of the included studies provided?							

(Continued)

A. Participants, interventions, exposure, and outcomes from the original studies provided in an aggregated form	Y	Y	Y	Y	Y	Y	Y
B. Ranges are provided of the relevant characteristics in the studies analysed	Y	Y	Y	Y	Y	Y	Y
C. Information provided appears to be complete and accurate	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4

7. Was the scientific quality of the included studies assessed and documented?

A. A priori methods are provided	Y	Y	Y	Y	Y	Y	Y
B. Scientific quality of the included studies appears to be meaningful	Y	Y	Y	Y	Y	Y	Y
C. Discussion, recognition, awareness of level of evidence is present	Y	Y	Y	Y	Y	Y	Y
D. Quality of evidence rated, ranked base on characterised instruments	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

A. Scientific quality considered in the analysis and the conclusions of the review	Y	Y	Y	Y	Y	Y	Y
B. Scientific quality is explicitly stated in formulating recommendations	Y	Y	Y	Y	Y	Y	Y
C. Conclusions integrated, drives towards practice guidelines	Y	Y	Y	Y	Y	Y	Y
D. Clinical consensus statement drives toward revision or confirmation of practice guidelines	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4

(Continued)

9. Were the methods used to combine the findings of studies appropriate?

A. Statement of criteria that were used to decide that the studies analysed were similar enough to be pooled	Y	Y	Y	Y	Y	Y	Y
B. For the pooled results, a test is done to ensure the studies were combinable, to assess their homogeneity	N	Y	Y	Y	Y	Y	Y
C. A recognition of heterogeneity or lack of there-of is present	Y	Y	Y	Y	Y	Y	Y
D. If heterogeneity exists, a random-effects model is used, the rationale of combining is taken into consideration, or both	Y	Y	Y	Y	Y	Y	Y
E. If homogeneity exists, a rationale or a statistical test is stated	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4

10. Was the likelihood of publication bias assessed?

A. Recognition of publication bias or file drawer effect	Y	Y	Y	Y	Y	Y	Y
B. Graphical aids (e.g. funnel plot)	N	N	N	N	N	N	N
C. Statistical tests (e.g. Egger regression test)	N	Y	Y	Y	Y	Y	Y
SCORE	2	3	3	3	3	3	3

11. Was the conflict of interest included?

A. Statement of sources of support	Y	Y	Y	Y	Y	Y	Y
B. No conflict of interest	Y	Y	Y	Y	Y	Y	Y
C. An awareness, statement of support or conflict of interest in the primary inclusion studies	N	N	N	N	N	N	N
SCORE	3	3	3	3	3	3	3

(Continued)								
TOTAL SCORE (out of 44)	41	41	42	42	40	40	40	

Footnotes

*Revised-Assessment of Multiple Systematic Reviews (R-AMSTAR) criteria

Y = Yes, criteria met (1 point), N = No, criteria not met (0 points)

Appendix 3. Quality assessment (R-AMSTAR) of included systematic reviews (Contd)

R-AMSTAR criteria*	Author year							
	Khan 2009	Khan 2015	Kopke 2014	Rietberg 2005	Rosti-Ota-järvi 2014	Sitjà Rabert 2012	Steultjens 2003	Thomas 2006
1. Was an a priori design provided?								
A. Clearly focused (PICO-based) question	Y	Y	Y	Y	Y	Y	Y	Y
B. Description of inclusion criteria	Y	Y	Y	Y	Y	Y	Y	Y
C. Study protocol published, registered in advance, or both	Y	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4	4
2. Was there duplicate study selection and data extraction?								
A. ≥ 2 persons independently extracted the data, explicitly stated	Y	Y	Y	Y	Y	Y	Y	Y
B. Statement of consensus procedure for disagreements	Y	Y	Y	Y	Y	Y	Y	Y
C. Disagreements among extractors resolved properly	Y	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4	4
3. Was a comprehensive literature search performed?								
A. At least two electronic sources are searched	Y	Y	Y	Y	Y	Y	Y	Y
B. Years & databases used are mentioned	Y	Y	Y	Y	Y	Y	Y	Y
C. Key words, MeSH terms (or both) are stated, and where feasible, the search strategy outline is provided	Y	Y	Y	Y	Y	Y	Y	Y

(Continued)

D. Searches are supplemented by consulting current contents, reviews, textbooks, registers, and by reviewing the references in the studies found	Y	Y	Y	Y	Y	Y	N	Y
E. Journals are handsearched or manual searched	Y	Y	N	Y	N	N	N	N
SCORE	4	4	4	4	4	4	3	4
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?								
A. Searched for reports regardless of their publication type	Y	Y	N	N	Y	Y	Y	Y
B. Any reports based on their publication status, language, etc. excluded	N	Y	N	N	N	N	N	N
C. Non-English papers were translated, or readers sufficiently trained in foreign language	N	Y	N	N	N	N	N	Y
D. No language restriction or recognition of non-English articles	N	Y	Y	N	Y	N	N	Y
SCORE	2	4	2	1	3	2	2	4
5. Was a list of studies (included and excluded) provided?								
A. Table, list, figure of included studies; a reference list does not suffice	Y	Y	Y	Y	Y	Y	Y	Y
B. Table, list, figure of excluded studies either in the article or in a supplemental source	Y	Y	Y	Y	Y	Y	Y	Y
C. Satisfactory, sufficient statement of the reason for exclusion of the seriously considered studies	Y	Y	Y	Y	Y	Y	Y	Y
D. Reader is able to retrace the included and the excluded studies anywhere in the article bibliography, reference, or supplemental source	Y	Y	Y	Y	Y	Y	Y	Y

(Continued)

SCORE	4	4	4	4	4	4	4	4
6. Were the characteristics of the included studies provided?								
A. Participants, interventions, exposure, and outcomes from the original studies provided in an aggregated form	Y	Y	Y	Y	Y	Y	Y	Y
B. Ranges are provided of the relevant characteristics in the studies analysed	Y	Y	Y	Y	Y	Y	Y	Y
C. Information provided appears to be complete and accurate	Y	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4	4
7. Was the scientific quality of the included studies assessed and documented?								
A. A priori methods are provided	Y	Y	Y	Y	Y	Y	Y	Y
B. Scientific quality of the included studies appears to be meaningful	Y	Y	Y	Y	Y	Y	Y	Y
C. Discussion, recognition, awareness of level of evidence is present	Y	Y	Y	Y	Y	Y	Y	Y
D. Quality of evidence rated, ranked base on characterised instruments	Y	Y	Y	Y	Y	Y	Y	Y
SCORE	4	4	4	4	4	4	4	4
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?								
A. Scientific quality considered in the analysis and the conclusions of the review	Y	Y	Y	Y	Y	Y	Y	Y
B. Scientific quality is explicitly stated in formulating recommendations	Y	Y	Y	Y	Y	Y	Y	Y
C. Conclusions integrated, drives towards practice guidelines	Y	Y	Y	Y	Y	Y	Y	Y

(Continued)

D. Clinical consensus statement drives toward revision or confirmation of practice guidelines	Y	Y	Y	Y	Y	Y	Y	Y
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SCORE	4	4	4	4	4	4	4	4
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9. Were the methods used to combine the findings of studies appropriate?

A. Statement of criteria that were used to decide that the studies analysed were similar enough to be pooled	Y	Y	Y	Y	Y	Y	Y	Y
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B. For the pooled results, a test is done to ensure the studies were combinable, to assess their homogeneity	Y	Y	N	N	Y	Y	N	Y
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C. A recognition of heterogeneity or lack of thereof is present	Y	Y	Y	N	Y	Y	N	Y
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D. If heterogeneity exists, a random-effects model is used, the rationale of combining is taken into consideration, or both	Y	Y	N	N	Y	Y	N	Y
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E. If homogeneity exists, a rationale or a statistical test is stated	Y	Y	N	N	Y	Y	N	Y
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SCORE	4	4	2	1	4	4	1	4
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10. Was the likelihood of publication bias assessed?

A. Recognition of publication bias or file drawer effect	Y	Y	Y	Y	Y	Y	N	Y
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B. Graphical aids (e.g. funnel plot)	N	N	N	N	Y	N	N	N
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C. Statistical tests (e.g. Egger regression test)	Y	Y	Y	N	Y	N	N	N
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SCORE	3	3	3	2	4	2	1	2
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11. Was the conflict of interest included?

A. Statement of sources of support	Y	Y	Y	Y	Y	Y	Y	Y
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(Continued)

B. No conflict of interest	Y	Y	Y	Y	Y	Y	Y	Y
C. An awareness, statement of support or conflict of interest in the primary inclusion studies	N	N	N	N	N	N	N	N
SCORE	3	3	3	3	3	3	3	3
TOTAL SCORE (out of 44)	40	42	38	35	42	39	34	41

Footnotes

*Revised-Assessment of Multiple Systematic Reviews (R-AMSTAR) criteria

Y = Yes, criteria met (1 point), N = No, criteria not met (0 points)

CONTRIBUTIONS OF AUTHORS

Task	Review author undertaking
Protocol stage	
Draft protocol	Bhasker Amatya, Fary Khan
Review of the protocol	All review authors
Review stage	
Study selection and data extraction	Bhasker Amatya, Fary Khan
Critical appraisals and analyses	Bhasker Amatya, Fary Khan
Interpretation of findings	All review authors
Review the content	All review authors
Draft final review	Bhasker Amatya
Update stage	
Update the review	All authors

DECLARATIONS OF INTEREST

The review authors are clinicians in the field of Physical and Medical Rehabilitation who wish to provide the best possible service to their patients.

Bhasker Amatya: none

Fary Khan: none

Mary Galea: none

The authors acknowledge that four included reviews were conducted by the present authors' team ([Amatya 2013](#); [Khan 2007b](#); [Khan 2009](#); [Khan 2015](#)), and one author (FK) was involved in another review ([Kopke 2014](#)).

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Internal sources

- Department of Rehabilitation Medicine, Royal Melbourne Hospital, Australia.

External sources

- None, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

*Physical Therapy Modalities; *Systematic Reviews as Topic; Controlled Clinical Trials as Topic; Multiple Sclerosis [*rehabilitation]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans